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| EXAMINER | |
|---|---|
| STRZELECKA, TERESA E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1637 | |

DATE MAILED: 01/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/086,917 | SOLLER ET AL. | |
| | Examiner | Art Unit | |
| | Teresa E Strzelecka | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12112002*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election of Group I (claims 1-17) in Paper No. 08092003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 18-21 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 08092003.

### *Information Disclosure Statement*

3. The information disclosure statement (IDS) submitted on November 12, 2003 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

### *Specification*

4. The disclosure is objected to because of the following informalities: on page 17, lines 11-13, Applicants incorporate by reference a co-pending application without identifying the application's number.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of developing a calibration model for transdermal spectroscopy

based on skin color or body fat index, does not reasonably provide enablement for a method of performing non-invasive measurement of any target analyte other than hemoglobin in patient's blood or tissue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-17 are broadly drawn to methods of performing non-invasive measurement of target analyte concentration in patient's blood using transdermal illumination. The type of analytes encompass all possible molecules present in tissues, such as different classes of proteins, DNA, RNA, tRNA, fatty acids, lipids, peptides, hormones, circulating drugs, and all classes of small molecules and their metabolites. However, as will be further discussed, there is no support in the specification and prior art for the methods as claimed, only for methods of deriving calibration models based either on skin color or body mass index, and to a method of obtaining hemoglobin spectra using the skin color calibration model. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The amount of direction or guidance presented

Applicants disclose a method for developing calibration spectra that can be applied to spectroscopic measurements of blood components. Specifically, Applicants describe methods to derive calibration spectra based on either skin color (page 13, paragraphs 3 and 4; page 14) or body mass index. Applicants state on page 15, second paragraph, that such a calibration model can be used for a calibration of spectral measurements of glucose, for example (second paragraph). Applicants showed in Example 1 (page 17, last paragraph; page 18-21) that calibration model obtained based on subjects' skin color can be used to determine hematocrit levels in subjects (page 21). On page 22, first paragraph, Applicants postulate using body mass index as another variability factor to be used in spectral correction, but do not demonstrate how such a model affects spectral measurements of any target analyte.

The presence or absence of working examples

No examples were presented which show the measurement of a wide variety of analytes present in the blood using calibration models based on a wide range of variability factors. Example 1 presents derivation of a calibration model based on skin color, and application of such model to the measurement of hematocrit (page 17, last paragraph; page 18-21). Applicants have not shown that such a calibration model can be used to determine concentrations of any other analytes in the blood, such as different classes of proteins, DNA, RNA, tRNA, fatty acids, lipids, peptides, hormones, circulating drugs, and all classes of small molecules and their metabolites. Applicants did not provide any examples of detection, for example, DNA, and discrimination of the DNA signal from any other nucleic acids. The claims encompass detection of all possible proteins as well. Applicants did not present the evidence that any single protein, such as p53, mucin or nuclear

proliferation factor, for example, could be detected against the background of all possible proteins present in the tissue under examination.

The unpredictability of the art and the state of the prior art

Measurement of analytes in the blood transdermally is based on the detection of reflected or transmitted light which is propagated through the skin. Near infrared spectroscopy is usually used for this purpose. However, the number of factors to be taken into account, and, consequently, to be included in the calibration, is very large and complex, including both spatial and temporal features. For example, as pointed out by Malin et al. (U.S. patent No. 6,280,381):

> "The absorbance of light at each wavelength is a function of the structural properties and chemical composition of the tissue. Tissue layers, each containing a unique heterogeneous particulate distribution, affect light absorbance through scattering. Chemical components, such as water, protein, fat and blood analytes, absorb light proportionally to their concentration through unique absorption profiles or signatures. The measurement of blood analyte concentrations is based on detecting the magnitude of light attenuation caused by the absorption signature of the targeted analyte. The process of calibration is the development of a mathematical transformation or model which estimates the blood analyte concentration from the measured tissue absorbance spectrum. However, accurate noninvasive estimation of blood analytes is presently limited by the dynamic nature of the sample, the skin and living tissue of the subject. Chemical, structural and physiological variations occur that produce dramatic changes in the optical properties of the tissue sample." (col. 1, lines 22-40).

Malin et al. list the following sources of spectral variation: 1) a large number of spectrally interfering species, 2) sample heterogeneity, related to tissue composition, 3) variations in subject's physiological state, related to hydration levels, changes of the volume fraction of blood in the tissue,

hormonal stimulation, temperature fluctuation, hemoglobin levels, 4) structural variations which include changes related to age, sex, environmental influences and body composition (col. 1, lines 63-67; col. 2, lines 1-45).

Khalil (Clin. Chem., vol. 45, pp. 165-177, 1999) reviewed spectroscopic and clinical aspects of noninvasive glucose measurements. Khalil shows data, obtained by several groups of researches, which indicate that tissue components such as water, hemoglobin, fat and protein have NIR bands in the same region as glucose (Table 1). Further, the effects of glucose on the absorption spectra of tissues are very small, "too small to allow for direct absorption measurements at wavelengths < 1400 nm. Attenuation of light (< 1400 nm) in a small body part such as an average-sized finger varies in the range 3-4 absorbance units, and the expected change in absorbance because of a 5mmol/L change in glucose concentration is $10^{-5}$ absorbance units" (page 169, first paragraph). Similar situation is found for light scattered from tissue (page 169, paragraphs 2-4).

Even though several groups have reported measurements of glucose concentrations in vivo (Table 6), however, as stated by Khalil "None of the NI experiments reviewed provides proof that the measured signal is related to the actual blood glucose concentration. The only indication is the existence of a correlation with the change in glucose concentration during the experiment." (page 173, last paragraph). Further, regarding calibration of the measurements, Khalil offers the following conclusion :

"Calibration has, thus far, relied on individual clinical calibration with an invasive reference method. Statistical analysis of calibration performance thus far has been insufficient to prove that NI calibration models derived from the reviewed spectroscopic techniques are based on glucose-specific information. Unless the physical effects producing the input data are understood, the

numerous factors needed to optimize the prediction of results raise the concern that these results may come from an overdetermined nonfunctional calibration model." (page 174, last paragraph).

Therefore, as can be seen from the above-cited references, determination of glucose concentration in tissue is still in the experimental stages because of the complexity of the system under study and inadequate calibration models. Further, as described by Khalil, NIR spectra of tissue constituents, such as proteins, are identical, therefore determination of a concentration of a single protein against such background would not be possible without development of additional technology.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this technology to in vivo methods. First, these parameters would have to be determined for all possible analytes to be determined in human tissue, such as different classes of proteins, DNA, RNA, tRNA, fatty acids, lipids, peptides, hormones, circulating drugs, and all classes of small molecules and their metabolites. Methods to detect DNA, and discrimination of the DNA signal from any other nucleic acids would have to be determined. The claims encompass detection of all possible proteins as well. Methods to detect proteins against the background of all possible proteins present in the tissue under examination would have to be determined. Such parameters include studying the effects of all tissue components which have absorbance bands in the same range as the desired analyte, effects of tissue hydration, blood volume, fat contents, hormonal influences, etc. These parameters would have to be studies separately for different physiological conditions, age differences, sex of the subjects and body compositions, for example. Further, calibration models for all of the above variables would

need to be determined and tested. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the absorption effects of any analyte in vivo depend upon numerous known and unknown parameters such as the structural and physiological properties of the tissues, heterogeneity based on age, sex and environmental factors, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the spectroscopic methods for in vivo determination of any analyte concentration. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-12 are indefinite in claim 1. Claim 1 is indefinite because the claim does not

recite a final process step which clearly relates back to the preamble. The preamble states that the method is for performing a non-invasive measurement of a target analyte present in patient's blood or tissue, but the final process step is "deriving spectral shapes corresponding to one or more variability factors based on said orthogonalized spectral measurements". Therefore, it is unclear as to whether the claim is intended to be limited to a method of non-invasive measurement of a target analyte present in patient's blood or tissue or a method of deriving spectral shapes corresponding to one or more variability factors based orthogonalized spectral measurements.

B) Claim 5 recites the limitation "the orthogonal spectral measurements" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 1, from which claim 5 depends, recites "orthogonalized spectral measurements".

C) Claims 13-16 are indefinite in claim 13. Claim 13 is indefinite because the claim does not recite a final process step which clearly relates back to the preamble. The preamble states that the method is for performing a non-invasive measurement of a target analyte present in patient's blood or tissue, but the final process step is "normalizing the collected spectra based on the derived spectral shapes to generate a set of corrected spectra". Therefore, it is unclear as to whether the claim is intended to be limited to a method of non-invasive measurement of a target analyte present in patient's blood or tissue or a method of normalizing the collected spectra based on the derived spectral shapes to generate a set of corrected spectra.

D) Claim 17 is indefinite because the claim does not recite a final process step which clearly relates back to the preamble. The preamble states that the method is for performing a non-invasive measurement of a target analyte present in patient's blood or tissue, but the final process step is "utilizing the corrected spectra to augment a calibration model". Therefore, it is unclear as to whether the claim is intended to be limited to a method of non-invasive measurement of a target

analyte present in patient's blood or tissue or a method of utilizing the corrected spectra to augment a calibration model.

***Claim interpretation***

9. The term "orthogonalization" has not been defined by Applicants. On page 18, third paragraph, Applicants use the term to describe subtracting background due to hematocrit from the spectra. Therefore, the term is interpreted as meaning any data processing. The term "chromophore" is interpreted as any light absorbing component. The term "spectral shape" is interpreted as a spectrum resulting from a spectral decomposition in a particular coordinate system.

***Claim Rejections - 35 USC § 102***

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-6, 10, 11, 13-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Malin et al. (U.S. Patent No. 6,280,381).

Regarding claims 1, 13 and 17, Malin et al. teach a system for measuring blood analytes non-invasively. The system performs non-invasive measurements of target analytes by near infrared (NIR) spectroscopy (col. 1, lines 11-20). The detection steps comprise the following steps:

compiling a database of spectral measurements for a plurality of subjects, the spectral measurements being taken transdermally by utilizing light (Malin et al. teach development of calibration models from the spectral absorbance of a population of subjects (col. 3, lines 4-7; col. 11, lines 3-10).),

orthogonalizing the spectral measurements to a known chromophore measured in each of the subjects, thereby producing a set of orthogonalized spectral measurements (Malin et al. teach extraction of simple features from the data, such as thickness of adipose tissue, magnitude of protein absorbance, scattering properties of the tissue, hematocrit levels, etc. col. 6, lines 50-67; col. 7, lines 1-50).), and

deriving spectral shapes corresponding to one or more variability factors based on said orthogonalized spectral measurements (Malin et al. teach spectral decomposition being used to determine features related to protein and fat absorbance spectra (col. 7, lines 52-58).

Regarding claim 2, Malin et al. do not specifically teach collecting the spectra with variation in the target analyte, but since the target analyte can be any molecule, and the spectra are collected from a representative number of subjects (col. 3, lines 4-7; col. 11, lines 3-10), Malin et al. teach this limitation.

Regarding claims 3, 12 and 17, Malin et al. teach generation of p different calibration models based on sets of features (col. 8, lines 35-42). In a fuzzy classification scheme, the classes are based on vectors of membership, rather than a strictly defined feature class (col. 11, lines 26-28). In this case, a given measurement of the calibration set impacts more than one calibration set, i.e., is used to augment and correct the already measured spectra.

Regarding claims 4 and 15, Malin et al. teach generating a calibration model based on the extraction of special features (col. 8, lines 10-67; col. 9, 10).

Regarding claim 5, Malin et al. teach deriving the calibration models using multivariate techniques, such as principal component regression, partial least square regression (col. 11, lines 10-16 and 61-67; col. 12, lines 15).

Regarding claims 6 and 14, Malin et al. teach variability factor being age (col. 7, lines 26-35).

Regarding claims 10 and 13, Malin et al. teach normalization of the collected spectra using the derived spectral shapes (Fig. 1; col. 10, lines 34-67).

Regarding claim 11, Malin et al. teach variability factor which relates to spectral characteristics due to environmental influences (col. 7, lines 49, 50).

Regarding claim 16, Malin et al. teach human contributing factors being fat content (col. 6, lines 55-63) or cell scattering (col. 7, lines 6-14).

***Claim Rejections - 35 USC § 103***

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malin et al. (U.S. Patent No. 6,280,381), Ruchti et al. (U.S. patent No. 6,587,702) and Weatherall et al. (J. Invest. Dermatol., vol. 99, pp. 468-473, 1992).

A) Teachings of Malin et al. are described above. Malin et al. do not teach the spectral shapes being derived from the CIELAB coordinates.

B) Ruchti et al. teaches determination of body composition using NIR. The teach that skin color causes large spectral variations at wavelengths below 1100 nm and represents a major confounding effect and source of bias (col. 4, lines 48-56).

C) Weatherall et al. teach measurements of skin color in terms of CIELAB color space

values, L , a* and b* (page 469, paragraphs 6-8; page 470, first paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the CIELAB skin color coordinates of Weatherall et al. in the methods of analyte concentration determination of Malin et al. and Ruchti et al. The motivation to do so, provided by Weatherall et al., would have been that "The description of the appearance of skin in these terms would give an objective measure of the visual perception of the colors and would have the additional advantage of enabling quantitative specification of the magnitude of perceived color differences or changes" (page 468, second paragraph).

14. No claims are allowed.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

The examiner will move to the new office in Alexandria on January 8, 2004. The new phone number in that office is (571) 272-0789. Gary Benzion will move to the new office on January 22, 2004. His new phone number is (571) 272-0782.

JEFFREY FREDMAN
PRIMARY EXAMINER

TS
January 8, 2004